REMARKS/ARGUMENTS

Claims 1-17, 19-21, 29, 30, and 33-46 have been examined in the above-identified application. Claims 18, 22-28, 31, 32 and 47-60 are withdrawn as being directed to a non-elected invention. Claims 45 and 61-63 are canceled without prejudice to continued prosecution of the subject matter encompassed by the claims in a related copending application. Claims 1, 3, and 34 have been amended. Claims 3 and 34 are amended to correct missing periods. Support for the amendments can be found in the specification; therefore, no new matter has been added. Reconsideration of the claims in light of the following remarks is respectfully requested.

Rejections Under 35 U.S.C. § 102:

Claims 1-2, 8-15, 42-43, and 45 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Mucke *et al.* (U.S. 6,175,057 B1, herein referred to as "Mucke"). According to the Examiner, Mucke discloses methods using transgenic animals or cells derived therefrom to identify candidate agents that modulate phenomena associated with Alzheimer's disease (AD) such as amyloid deposition (which results inherently from the processing of amyloid precursor protein (APP)). The Examiner alleges that these candidate agents are disclosed as being from compound libraries, combinatorial libraries, natural product libraries, small molecules, biomolecules, and peptides (instant claims 8-15). The Examiner further submits that labeled antibodies may be used to quantify amyloid proteins in neurite plaques or cells (instant claims 42-43). In addition, the Examiner alleges that allosteric effectors of APP would be identified by the prior art methods as inherently as other inhibitors would be identified by the prior art methods (the process steps of the screening assay are capable of identifying a broad genus of inhibitors).

Applicants respectfully disagree with the rejection and traverse below. To expedite prosecution of the present case, claim 1 has been amended to more clearly and distinctly claim certain aspects of the present invention. As amended, claim 1 is directed to a method for identifying an agent that alters processing of β-amyloid precursor protein (APP) comprising:

contacting the agent with an animal host cell that expresses APP and at least one APP processing enzyme; detecting altered APP processing to identify the agent that alters the processing of APP; and, identifying the agent that is an allosteric effector of APP. Support for the amendments can be found, for example, in the published application at paragraph [0132]. Furthermore, as paragraph [0132] indicates, there is no required order for carrying out the presently claimed method steps. For instance, identification of allosteric effectors can be performed as a secondary screen on agents that have been identified as effectors of membrane protein processing. Alternatively, libraries can be prescreened to identify allosteric effectors, prior to carrying out the other claimed steps of contacting the agents to the cells and detecting altered processing of the membrane protein.

Applicants submit that Mucke cannot anticipate the present claims because, for example, each and every element is not taught (either expressly or inherently) by the reference. First, while Mucke does disclose general information about drug screening assays well known to the skilled artisan, the reference makes no mention of an agent that is an allosteric effector whatsoever. Therefore, the reference does not expressly teach each and every element of present claims. Second, Applicants disagree that the discovery of allosteric effectors using the method of Mucke are inherent and respectfully believe that the rejection is improper. For instance, the Examiner asserts that the process steps of the methods in Mucke are capable of identifying a broad genus of inhibitors and that allosteric effectors of APP would be identified. Applicants note that such a general rejection on the basis of inherency is improper. For example, the Court has held that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category." MPEP 2112 (citing *Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004)). Thus, even if allosteric inhibitors of an enzyme substrate were a species of the alleged broad genus of inhibitors, they would not be inherently disclosed by Mucke. Furthermore, the MPEP clearly states the following:

> To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference,

> and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. MPEP 2112 (citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (quotations and citations omitted).

The Examiner provides no extrinsic evidence, basis in fact, and/or technical reasoning that clearly points out that allosteric effectors of the enzyme substrate APP would be identified using the general disclosures of Mucke. At most, it is only a mere possibility that such screening assays might identify allosteric effectors of APP. In view of the present invention though, it is actually unlikely that allosteric effectors of APP would be identified using the methods disclosed by Mucke. For example, the presently claimed method includes both screening to detect altered processing as well as to identify allosteric effectors that associate specifically with the enzyme substrate APP. The methods described in Mucke do not teach or suggest an additional step of identifying allosteric effectors of APP and, thus, would not likely give results that corresponded to allosteric effectors. For at least the reasons set forth above, the reference cannot anticipate the present claims. Accordingly, Applicants respectfully request that the Examiner to reconsider and withdraw the rejection to claims 1-2, 8-15, 42-43, and 45 under 35 U.S.C. § 102(b) as anticipated by Mucke *et al.*

Claims 1-7, 36-39, and 45-46 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Gurney *et al.* (US 6,440,698 B1, herein referred to as "Gurney"). The Examiner believes that Gurney discloses methods for identifying inhibitors of an enzyme that cleaves the β-secretase cleavable site (instant claims 3-4) of amyloid precursor protein (APP) from an animal host cell that expresses APP and β-secretase and measuring the release of amyloid beta-peptide (Aβ) into the culture medium and accumulation of C-terminal fragments (CTF99) in cell lysates (instant claim 2). The Examiner submits that Aβ1-42 peptide is a form of Aβ peptide disclosed as being particularly amyloidogenic and thus very important in Alzheimer's Disease (AD) (instant claims 5-7). According to the Examiner, Gurney also teaches recombinant animal isolated host cells (instant claims 36-38) used in the instant methods, the use of a flow sorter (instant claim 46), and carrying out the method with living cells in a culture medium (instant

claim 39). The Examiner alleges that allosteric effectors of APP would be identified by the prior art methods as inherently as other inhibitors would be identified by the prior art methods (the process steps of the screening assay are capable of identifying a broad genus of inhibitors).

Applicants respectfully disagree with the rejection and traverse below. As indicated above, claim 1 is directed to a method for identifying an agent that alters processing of β-amyloid precursor protein (APP) comprising: contacting the agent with an animal host cell that expresses APP and at least one APP processing enzyme; detecting altered APP processing to identify the agent that alters the processing of APP; and, identifying the agent that is an allosteric effector of APP. First, while Gurney may disclose, for example, methods related to assaying for modulators of β-secretase activity, an enzyme that cleaves APP and other proteins, the reference makes no mention of allosteric effectors of the enzyme substrate APP whatsoever. Therefore, the reference does not expressly teach each and every element of present claims. Second, Applicants disagree with the Examiner's inherency argument regarding allosteric effectors and respectfully believe that the rejection is improper. For instance, the Examiner asserts that if the methods in Gurney allegedly can identify a broad genus of inhibitors then they can allegedly identify allosteric inhibitors. Applicants disagree with this reasoning. In particular, the Court has found that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category." MPEP 2112 (citing *Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004)). Thus, even if allosteric inhibitors might be a species of effectors identified in the broad genus of inhibitors found by the methods of Gurney, they would not be inherently disclosed. Particularly, Gurney is not directed to methods that identify allosteric effectors of the enzyme substrate APP. Furthermore, the MPEP clearly states the following:

> To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. MPEP 2112 (citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (quotations and citations omitted).

The Examiner has provided no extrinsic evidence, basis in fact, and/or technical reasoning that clearly points out that allosteric effectors of the enzyme substrate APP would be identified using the methods taught by Gurney, or any other known method. At most, it is only a mere possibility that such screening assays might identify allosteric effectors of the enzyme substrate APP. In view of the present invention though, it is actually unlikely that allosteric effectors of APP would be identified using the prior art methods. For example, the presently claimed method includes both screening to detect altered processing as well as to identify allosteric effectors that associate specifically the enzyme substrate APP. The methods described in Gurney do not teach or suggest any step for identifying allosteric effectors of the enzyme substrate APP and, thus, would not likely give results that corresponded to allosteric effectors of APP. Identifying allosteric effectors of APP using the methods of Gurney is not inherent. Therefore, for at least the reasons set forth above, the reference cannot anticipate the present claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection to claims 1-7, 36-39, and 45-46 under 35 U.S.C. § 102(e) as anticipated by Gurney *et al.*

Rejections Under 35 U.S.C. § 103:

Claims 1, 13-17, 19-21, 29, and 33-35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gurney in view of Nolan (US 2002/0127564). The Examiner points to the § 102(e) rejection above to define Gurney's teaching. According to the Examiner, Gurney does not teach a method of identifying peptide agents/inhibitors wherein the peptide is encoded by oligonucleotides of about 18 to about 120 nucleotides or of about 36 to about 60 nucleotides. The Examiner asserts that Nolan teaches methods for identifying bioactive agents from translation products (instant claims 13-15) ranging from about 4 amino acids in length (equivalent to about 12 nucleotides) to about 100 amino acids in length (equivalent to about 300 nucleotides). The Examiner submits that especially preferred embodiments are about 18 to about 60 nucleotides in length (instant claims 16-17) and that said nucleotide sequences of Nolan can be from expression libraries comprising randomized expression products, and include a fusion presentation partner (instant claims 19-20 and 29). Furthermore, the Examiner alleges that this fusion protein can comprise marker epitopes such as polyhistidine and myc (instant claims 33-

34) or a membrane anchoring glycophosphatidylinositol (GPI) (instant claim 35). According to the Examiner, it would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney for screening of inhibitors of an enzyme that cleaves the β-secretase cleavable site of APP from an animal host cell that expresses APP and by using the encoded peptides with sequence length as suggested by Nolan because Nolan discloses that small peptides (that is, peptides encoded by about 18 to about 60 nucleotides in length) can be conformationally constrained into "presentation structures" which "will benefit both the later generation of pharmaceuticals and will also likely lead to higher affinity interactions with the peptide with the target protein;" the target protein, being in the instant case, β-secretase. Furthermore, the Examiner alleges that it would also be obvious to try to use expression libraries that are pre-enriched for oligonucleotides encoding peptides that specifically bind to APP because the aim of the teachings of Gurney is to find inhibitors of APP processing in order to treat AD, and peptides that bind to APP would have the capability of interfering with the binding of β-secretase to APP and block the enzyme from cleaving the APP substrate. The Examiner asserts that the advantage of small peptides that Nolan teaches renders instant claims 1, 13-17, 19-21, 29, and 33-35 *prima facie* obvious in conjunction with Gurney.

Applicants respectfully disagree with the rejection set forth by the Examiner. Applicants submit that the cited references, when considered either alone or in any combination, would not have suggested nor predicted with a reasonable expectation of success each and every element of the present claims. For example, as set forth above, Gurney generally discloses methods related to assaying for modulators of β-secretase activity; however, the reference fails to teach or suggest methods for identifying allosteric effectors of the enzyme substrate APP. As such, Gurney does not explicitly disclose a method as presently claimed. In addition, Gurney can not inherently disclose a species of an invention by only disclosing the general aspects of a generic invention. Particularly when only disclosing methods for identifying modulator of the enzyme β-secretase. As such, Gurney fails to disclose the method as currently claimed. Nolan fails to provide any missing element of Gurney. Nolan is directed to a method for screening generally for a transdominant intracellular bioactive agent capable of altering the phenotype of a

cell; the reference makes no mention of allosteric effectors of an enzyme substrate, such as APP, whatsoever. Therefore, even if one of ordinary skill in the art were to attempt to combine the references, the combination would not yield the present claims directed to a method for identifying an agent that alters processing of APP that includes a step of identifying agents that are allosteric effectors of the enzyme substrate APP. Finally, the Examiner believes that it would have been obvious to try to use expression libraries pre-enriched for oligonucleotides encoding peptides and further concludes that peptides would bind to APP and interfere with binding to β-secretase. As stated in MPEP 2143, however, obvious to try relates to choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. Applicants believe that the Examiner has asserted an improper "obvious to try" standard in framing this rejection and, furthermore, the Examiner has provided no reasoning or basis as to why one of ordinary skill in the art would have had a reasonable expectation of success for identifying peptides that bind to APP let alone whether any binding molecules were allosteric effectors of APP. In view of the reasons above, the present claims are not believed to be obvious in light of Gurney and/or Nolan when considered alone or in any combination. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw of the rejections of claims 1, 13-17, 19-21, 29, and 33-35 under 35 U.S.C. § 103(a) as unpatentable over Gurney *et al.* in view of Nolan.

Claims 1, 13-15 and 29-30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gurney in view of Nolan (US 2002/0127564, herein referred to as "Nolan") and further in view of Poncet *et al.* (*Acta. Neuropathol.* 91:400-408, 1996, herein referred to as "Poncet"). The Examiner's alleged teachings of Gurney and Nolan are as set forth above. Additionally, the Examiner alleges that Nolan teaches membrane anchoring sequences such as the glycosylphosphatidylinositol (GPI) anchor, which can be used to target particular peptides to the cell membrane so that the target peptides can interact with other membrane proteins. According to the Examiner, Nolan does not teach the specific CD24 presentation molecule which has a GPI anchor. The Examiner submits that Poncet teaches the CD24 presentation molecule, including its GPI anchor, and that Poncet further discloses that CD24 is expressed by human

brain neurons. Applicants note that the office on line 1 of page 7 appears to have an editing error. Applicants are uncertain of the exact rejection and reasoning of the Examiner; however, in order to further expedite prosecution of the applications, Applicants have assumed that based on similar allegations in the previous rejection that the rejection is directed to the "β-secretase cleavage site." If this assumption is incorrect, Applicants request further clarification. In addition, the Examiner submits that absent evidence to the contrary, it would have been obvious to select CD24 as a GPI anchor presentation molecule because the invention is drawn to screening therapeutic agents for AD which only occurs in humans and CD24 is a naturally occurring GPI anchor in human neurons.

Applicants respectfully disagree with the rejection as set forth by the Examiner. Applicants submit that Gurney, Nolan and Poncet, when considered either alone or in any combination, would not have suggested nor predicted with any reasonable expectation of success each and every element of the present claims. For example, as set forth above, Gurney discloses methods related to generally assaying for "modulators" of β-secretase activity; however, the reference fails to teach or suggest identifying allosteric effectors of the enzyme substrate APP. In addition, as already noted above, Nolan fails to provide the missing elements of Gurney; Nolan (like Gurney) generally discloses certain peptides that are intracellular modulators of APP but makes no mention of allosteric effectors of APP whatsoever. While Poncet teaches that CD24 is a glycoprotein that links to the outer surface of the plasma membrane by a glycosylphosphatidylinositol (GPI) lipid anchor, the reference also fails to teach or suggest allosteric effectors of APP or any methods including a step of identifying allosteric effectors of APP. Therefore, even if *in arguendo* one of ordinary skill in the art were to attempt to combine the references, the combination would not yield a method for identifying an agent that alters processing of APP that includes a step of identifying agents that are allosteric effectors of the enzyme substrate, APP. In view of the reasons above, the present claims are not believed to be obvious in light of Gurney, Nolan, and/or Poncet. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 1, 13-15, and 29-30 under 35

U.S.C. § 103(a) as being unpatentable over Gurney, in view of Nolan, and further in view of Poncet.

Claims 1 and 39-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gurney and Nolan as applied to claims 1, 13-17, 19-21, 29, and 33-35 above, and further in view of Mazur-Kolecka *et al.* (*J. Neuropathol. Exp. Neurol.*, 56:263-272, 1997, herein referred to as "Mazur-Kolecka"). The Examiner submits that Gurney and Nolan do not teach methods using blood serum or CSF. The Examiner further asserts that Mazur-Kolecka does teach methods of studying β-amyloid processing and deposition using both serum and CSF and Mazur-Kolecka discloses the differential effects of each on the assay methods. According to the Examiner, it would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney and Nolan for screening of inhibitors of an enzyme that cleaves the β-secretase cleavable site of APP from an animal host cell that expresses APP and β-secretase by also including the use of serum or CSF in the assay system because Mazur-Kolecka disclose that the presence of serum can worsen the disease process while the presence of CSF can lessen the disease process of β-amyloid processing and deposition. The Examiner alleges that because such information would be relevant for the clinical development of therapeutic agents, the teachings of Mazur-Kolecka render the instant claims *prima facie* obvious.

Applicants respectfully disagree with the rejections set forth by the Examiner. Applicants submit that Gurney and Nolan, further in view of Mazur-Kolecka, when considered either alone or in any combination, would not have disclosed, suggested, nor predicted with any reasonable expectation of success each and every element of the present claims. In particular, as set forth above, Gurney discloses general methods related to assaying for modulators of β-secretase activity; however, the reference fails to teach or suggest identifying allosteric effectors of a the enzyme substrate APP. In addition, as already noted above, Nolan fails to provide any element missing from Gurney. Particularly, Nolan is directed to different general methods of screening intracellular agents that alter the phenotype of non-human transgenic animals. The agents can be peptides encoded by random nucleotide sequences. However, Nolan, (like

Gurney) provides no teaching or even suggestion of allosteric effectors of an enzyme substrate whatsoever. Much less allosteric effectors of the enzyme substrate membrane protein (APP). While Mazur-Kolecka examines the influence of sera and cerebrospinal fluid on intracellular accumulation of Aβ-immunoreactive deposits and on secretion of soluble Aβ into culture media, the reference does not provide any teaching or suggestion of allosteric effectors of a secretase let alone methods for identifying allosteric effectors of APP. Therefore, even if one of ordinary skill in the art were to attempt to combine the references, the combination would not yield the presently claimed method for identifying an agent that alters processing of APP that includes a step of identifying agents that are allosteric effectors of the enzyme substrate. In view of the reasons above, the present claims are not obvious in light of Gurney and Nolan, in further view of Mazur-Kolecka when the references are considered alone or in any combination. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejections of claims 1 and 39-41 under 35 U.S.C. § 103(a) as being unpatentable over Gurney and Nolan, in further view of Mazur-Kolecka.

Claims 1-2 and 42-45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gurney in view of Mucke. The Examiner's alleged teachings of Gurney and Mucke are as set forth above. Additionally, the Examiner asserts that Gurney teaches methods using at least two different antibodies for at least two different epitopes of APP and generating standard curves for quantifying amyloid peptides from cell culture supernatants. According to the Examiner, Gurney does not teach double antibody methods involving the cell surface. The Examiner asserts that Mucke does teach quantifying amyloid peptides by using antibodies at the cell surface. The Examiner believes that it would have been obvious at the time the invention was made for one of ordinary skill in the art to use the methods of Gurney for screening of inhibitors of an enzyme that cleaves the β-secretase cleavable site of APP from an animal host cell that expresses APP and β-secretase with double antibodies for different epitopes at the cell surface as taught by Mucke in order for Gurney to confirm and correlate the various amounts and ratios of different APP products that are produced in the assay system as a control to make sure the assay system is accurate, *i.e.*, the amounts of soluble fragment released should correlate with

the amount of APP fragments left behind in the cell membrane. The Examiner further believes that allosteric effectors of APP would be identified by the prior art methods as obviously as other inhibitors would be identified by the prior art methods (the process steps of the screening assay are capable of identifying a broad genus of inhibitors).

Applicants respectfully disagree with the rejections set forth by the Examiner. With regards to the rejections of claims 1, 2, and 42-44, Applicants submit that the cited references, when considered either alone or in any combination, would not have suggested nor predicted with a reasonable expectation of success each and every element of the present claims. For example, as set forth above regarding the alleged anticipation of the claimed invention by Gurney, Gurney discloses methods related to assaying generally for modulators of β-secretase activity; however, the reference fails to teach or suggest identifying allosteric effectors of an enzyme substrate, such as APP. In addition, as already noted above, Mucke fails to provide the missing elements of Gurney; Mucke (like Gurney) makes no mention of allosteric effectors whatsoever, much less an allosteric effector of an enzyme substrate. Therefore, even if *arguendo* one of skill were to attempt to combine the references, the combination would not yield the presently claimed method for identifying an agent that alters processing of APP that includes a step of identifying agents that are allosteric effectors of the enzyme substrate, APP.

Applicants note that claim 45 has been canceled without prejudice. In view of the amendments and reasons set forth above, claims 1 and 42-44 are not believed to be obvious in light of Gurney and Mucke. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejections of claims 1 and 42-45 under 35 U.S.C. § 103(a) as unpatentable over Gurney in view of Mucke.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an

early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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